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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/030,605	FIEDLER ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7,9-11,14,16,26-28,42 and 47-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7,9-11,14,16,26-28,42 and 47-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/16/2008 has been entered.

Status of Claims

1. Claims 42, 47 are amended and claims 48-57 are added. Claims 12,15,43-46 are canceled. Claims 5-7,9-11,14,16,26-28,42,47-57 are pending.

Claim Objections

2. Claims 42, 47,54 are objected for the following informalities: It seems that the phrase "the amino acids that are mutagenized are located in two-three, or **for**" is intended to read as "the amino acids that are mutagenized are located in two-three, or **four**" . Please correct.

Claim Rejections - 35 USC 112, first paragraph (written description)

2. Claims 5-7,9-11,14,16,26-28,42,47,54-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The breadth of claims 42,47,16 and claims 5-7,9-11,14,16,26-28 dependent on claim 42, encompasses any mutagenized gamma-crystallin polypeptide having surface-located residues of at least two (and up to four) beta strands of at least one beta sheet (there are four beta sheets in gamma crystallin) mutagenized is such way that the mutant possesses a new binding activity which did not exist in the parent protein. A mutation may be either any insertion, deletion, substitution, or any combination thereof.

The claimed genus of mutant proteins is represented by two mutants of gamma-II-crystalline of SEQ ID No. 22 having the same each having the same highly specific mutation, namely mutation of seven residues K3,T5,Y7,C16,E18,S20,D39 into R3,K5,K7,Y16,S18,N20,L39, respectively. These mutated residues happen to be located in the first three beta strands of the first (from N-terminal end) beta sheet of gamma-crystallin. Only this particular mutation results in acquiring “a new binding activity” towards a specific binding partner BSA-estradiol-17-hemisuccinate. Said R3,K5,K7,Y16,S18,N20,L39 mutants having binding affinity toward BSA-estradiol-17-hemisuccinate were identified after screening of 26 billion (!) mutants (p. 13, last two paragraphs). There are no indication that the applicant was in possession of any other

gamma-crystallin polypeptide of the broad genus as claimed which possessed a new binding activity to any binding partner as well. The above two mutants having a very particular seven-residue substitution, are not sufficiently representative of the genus of any mutants of proteins encompassed by the claims; they are not sufficient to reasonably convey to one skilled in the relevant art that the inventors had possession of the entire genus of the mutants as claimed. For example, specification does not convey that applicants were in possession of mutant gamma-crystallin polypeptide demonstrating "a new binding activity" wherein the mutant has mutations in two, or four stands, or wherein the mutant has mutations in any other of "at least one beta-sheet", or wherein the mutant has any substitutions other than described for the above mutants, or wherein the mutant has deletions of residues, or wherein the mutant has insertion of residues, or wherein the mutant has a random combination of insertion, deletion, substitution, etc.

Further, the claimed mutants are addressed as having a functional limitation of having "a new binding activity" towards a[ny] binding partner. The only binding partner disclosed for the mutants addressed above is BSA-estradiol-17-hemisuccinate. The generally stated functional limitation of having "a new binding activity" towards any binding partner does not provide sufficient structural characteristics to define the genus of the claimed proteins. Note, that the claims are directed to products, not to a method of making.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cat*h, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that besides one very specific mutant containing mutations at seven particular locations of bovine gamma II crystallin and having binding affinity for particular binding agent, BSA-estradiol-17-hemisuccinate, applicants generated any other crystalline protein having new characteristics other than ability to bind BSA-estradiol-17-hemisuccinate. Much less there is any demonstration in the specification of any other protein which, being mutagenized, appropriated new functional characteristics as claimed.

Further, with regard to claims 50, 54-57 the breadth of the claims is the same except that it is limited to one, N-terminal, beta-sheet . Even though the scope of this subgenus is smaller, the two mutants having a very particular seven-residue substitution described above are not sufficiently representative of this subgenus of any mutants of proteins encompassed by the claims; they are not sufficient to reasonably convey to one skilled in the relevant art that the inventors had possession of the entire subgenus of the mutants as claimed.

Response to arguments

Applicant argues that amendment of the claims to recite residues located on the surface of the protein overcomes the rejection. Examiner disagrees. The two mutants having a very particular seven-residue substitution and very particular functional activity as described above are not sufficiently representative of the genus that encompasses any gamma-crystallin polypeptide having surface-located residues of at least two (and up to four) beta strands of at least one beta sheet mutagenized by insertion, deletion, substitution, or any combination thereof is such way that the mutant possesses a[ny] new binding activity which did not exist in the parent protein.

Applicant further argues that residues that are located on the surface of the protein “are few in number”. Nowhere in specification there is a description of a limited and “few in number” subgenus of residues to be mutated, nor there is any description of amount of residues that are surface-located, in general. The arguments of councel can not take the place of evidence in the record.

Further, applicant argues that the seven residue-substitution demonstrated in the specification would inform an artisan which residues would be appropriate for mutagenesis because there is a "high degree" of amino acid sequence conservations among gamma-crystallins. First, specification while addressing similar domain structures (p. 4), does not provide evidence for "high degree" of amino acid sequence conservations among gamma-crystallins. Second, the description of a very particular seven-residue substitution does not provide sufficient written description for any substitutions, and much less for deletions an/or insertions. Third, the particular seven-residue substitution resulting in a specific binding affinity towards BSA-estradiol-17-hemisuccinate does not provide sufficient written description for mutants having specific binding activity towards any other binding partners. The point of the rejection is not only that there is no sufficient written description demonstrating possession of the entire genus of gamma-crystallin mutants, but also lack of description of possession of genus of mutants of gamma-crystallin polypeptides demonstrating "a new binding activity".

Claim Rejections - 35 USC § 112, first paragraph (enablement).

The following rejection is modified in view of applicant's comments and amendments to the claims.

4. Claims 5-7,9-11,14,16,26-28,42,47,54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutants of bovine gamma crystallin of SEQ ID No. 22 obtained by mutations at positions identified in claim 12, does not reasonably provide enablement for mutants of other crystallins, much less for other proteins with mutations at beta sheet structure as claimed.

The breadth of claims 42,47,16 and claims 5-7,9-11,14,16,26-28 dependent on claim 42, encompasses any mutagenized gamma-crystallin polypeptide having surface-located residues of at least two (and up to four) beta strands of at least one beta sheet (there are four beta sheets in gamma crystallin) mutagenized is such way that the mutant possesses a new binding activity which did not exist in the parent protein. A mutation may be either any insertion, deletion, substitution, or any combination thereof. The breadth of claims 50, 54-57 is the same except that it is limited to one, N-terminal, beta-sheet.

Specification exemplifies the invention by disclosing mutants of gamma-II-crystalline of SEQ ID No. 22. Specification teaches that the initial protein, gamma-II-crystalline "has no binding properties whatsoever" (p. 4, second paragraph). For this protein, eight particular residues located in three beta strands on the surface were selected and randomized by site-specific mutagenesis. Out of 26 billion (!) mutants generated (p. 13, last paragraph) only one "expected amino acid exchanges" is discovered (p. 13, third full paragraph). Seven residues K3,T5,Y7,C16,E18,S20, and D39 have the same mutation to R3,K5,K7,Y16,S18,N20, and L39 in the two mutants obtained, SEQ ID No. 19 and 21. Except for gamma-II-crystalline SEQ ID No. 22,

specification does not provide any working examples of any other mutants of crystallins mutated at any other residues than the residues indicated for SEQ ID No. 22.

Except for being located in β strands on the surface of the protein, no guidance is provided for selecting a number and/or location of residues to be mutated. The eight residues selected for mutation are described as forming "a continuous surface segment" which happened to be located in three beta strands (Sheme B), no guidance is offered of selecting particular residues from those located in "at least two beta strands" as claimed; nor there is any guidance on whether to proceed with substituting or depleting such residues, or inserting new residues. Further, the mutants of the invention, as now claimed, have functional limitation of having new or improved antigen binding specificity towards a binding partner. Specification does not provide guidance on how to select residues suitable for mutagenesis to yield a mutant with "antibody-like" binding activity towards a particular partner of interest.

For comparison, in a similar method of creating mutant antibody-like proteins derived from lipocalin, Beste et al, first developed a set of criteria to identify residues suitable for random mutagenesis to achieve binding to a non-natural ligand: location in natural ligand-binding pocket, ability to contact a natural ligand, and non-interference with residues forming hydrophobic core. No such guidance is offered with respect to mutants as instantly claimed.

It is well known in the art that it is difficult to predict the functional effects of random single amino acid substitutions, and nearly impossible to predict the functional

effects of multiple amino acid substitutions. The relationship between the sequence of a peptide and its tertiary structure (and thus its binding activity) are not well understood and are not predictable (see Ngo et al.).

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make the invention with the claimed breadth without an undue amount of experimentation.

Response to arguments

Applicant argues that specification includes specific recitation of amino acids that can be mutagenized to arrive at claimed subject matter, as exemplified on page 17. Examiner disagrees. p. 17 points at residues of a particular sequence of gamma-II-crystaline1. The rejection being applied is a scope of enablement rejection. All that is demonstrated in the specification is very specific permutation of seven mutations of residues K3,T5,Y7,C16,E18,S20, and D39 of SEQ ID No. 22. The showing on p. 17 is not commensurate with the scope of the invention as claimed in broad claims 42,47,48, 54,56.

Further, applicant traverses what is cited to be Examiner's assertion that the term "[a surface of the protein] would not be understood by one skilled in the art". There was no such discussion that the term would not be understood by one skilled in the art in the

rejection. Rather, the issue is that because there is no definition of the term "surface", any residue of polypeptide's sequence is considered to be a "surface residue". As for citing the same paragraph on p. 17[2] , as addressed above, the showing on p. 17 is not commensurate with the scope of the polypeptides encompassed by the invention.

The mutants of the invention have functional limitation of having a new binding activity towards a binding partner. Specification does not provide guidance on how to select residues suitable for mutagenesis to yield a mutant with a binding activity towards a particular partner of interest.

Claim Rejections - 35 USC э 112, first paragraph (New matter).

Upon review of residue numbers of SEQ ID No. 22 as addressed in the claims, compared to the same information in specification, the following rejection was deemed necessary:

Claims 48,49,51-53, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 48,51 introduce new matter as they address residues with residue numbers that are not addressed in the same way in specification. Each residue number is shifted up by one in the claims

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1 It is noticed that the position numbers of the residues differ, by one, from those instantly claimed.

2 Said paragraph, again addresses residues having position numbers of the residues differ, by one, from those instantly claimed

(e.g., Lys 3 in the claims compared to Lys 2 in specification); compare claim 51 and specification, p. 17, for example. Further, the original claims (see claim 12 of the version of 01/09/2002, for example) were in conformance with the specification. Thus, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC 102

9. Claims 5-7,9-11,16,26-28,42,47 are rejected under 35 U.S.C. 102(a) as anticipated by Beste et al. (the reference was first applied in the first Office action on merits mailed 02/15/2005)

Beste teaches that lipocalin mutants. Lipocalins share a conserved β-barrel of eight antiparallel β-strands as their central folding motif. At one end of this supersecondary structure four loops connect each pair of β-strands and form the entrance to the binding pocket. The binding site is formed by four loops on top of an eight-stranded β-barrel. p. 1898. 16 residues spread across the four loops and adjoining parts of the β-barrel of a lipocalin from *Pieris brassicae*, the bilin-binding protein (BBP), were selected and subjected to random mutagenesis. p. 1900, right column. The 16 positions were mutagenized in a polymerase chain reaction and a genetic library with $3.7 \cdot 10^8$ independent transformants was obtained. Out of those, four variants having a

new feature, ability to bind fluorescein, a fluorophore and immunological hapten, were selected. p. 1901, left column. The reference also teach a composition - solution of ELISA binding assay (p. 1900, left column).

The mutants of Beste are viewed as reading on the mutant proteins of the instant invention because:

1. They are viewed as a result of multiple insertions, deletions, and substitutions of the sequence of gamma-crystallin. Note, no limit to the amount of insertions deletions, substitutions, or any combination thereof., is set in the instant claims.
2. They comprise mutations in beta strands of beta sheets.
3. They possess binding activity not known for crystallins.

With respect to claims 5-7,9-11,26-28 directed to various originating proteins to be mutagenized, the protein of Beste is viewed as a result of multiple mutations of any of those proteins.

With respect to claim 47,, the claim is in product-by-process format, and as such, it is the novelty and patentability of the instantly claimed product that need to be established and not that of the recited process steps. In re Brown, 173 USPQ 685 (CCPA 1972); In re Wertheim, USPQ (CCPA 1976).

Conclusion.

No claims are allowed

Claims 48,49, if rewritten to overcome the rejection under 35 U.S.C. § 112, would be allowable over the prior art of record or any combination thereof. Similarly, claims 51-53 would be allowable if rewritten to overcome the rejection under 35 U.S.C. § 112 and to include all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./

Primary Examiner, Art Unit 1631